## II. REMARKS

**Formal Matters**

Claims 26 and 28-36 are pending after entry of the amendments set forth herein.

Claims 26-36 were examined and were rejected.

Claim 26 is amended. The amendment to claim 26 was made solely in the interest of expediting prosecution, and is not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendment to claim 26 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 9, lines 27-29; and page 13, lines 11-12. Accordingly, no new matter is added by these amendments.

Claim 27 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C. §112, first paragraph

Claims 26-36 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 26-36 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

Claims 26-36; written description

The Office Action stated that the specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the very broad genus comprising EGF-R antagonists, and which provide for the function of treating nasal polyps in a subject. Applicants respectfully traverse the rejection.

The specification provides ample description of EGF-R antagonists. Specification, page 7, line 21 to page 8, line 23. Many of the EGF-R antagonists discussed in the specification are known to those skilled in the art. The general classes of EGF-R antagonists described in the specification include tyrosine kinase inhibitors, antibodies that bind a factor that stimulates EGF or EGF-R production, e.g., an antibody to TGF-α.

The specification provides working examples of at least three different EGF-R antagonists: two different tyrosine kinase inhibitors, as well as an antibody to TGF-α. For example, the specification provides working examples that BIBX1522, a tyrosine kinase inhibitor that is an EGF-R antagonist, inhibits MUC5AC production in cultured cells *in vitro* and inhibits mucus hypersecretion *in vivo*. Specification, e.g., Example 1. The specification further provides a working example showing that AG1478, another tyrosine kinase inhibitor that is an EGF-R antagonist, prevented MUC5AC synthesis induced by an activator of EGF-R, and inhibited EGF-R phosphorylation. Specification, e.g., Example 2. AG1478 and BIBX1522 inhibit goblet cell hyperplasia. The specification further provides a working example showing that a TGF-α neutralizing antibody reduced stimulation of the EGF-R and reduced production of goblet cells. Specification, e.g., Example 3.

As such, the specification provides ample written description.

Nevertheless, and solely in the interest of expediting prosecution, 26 is amended to recite "wherein the EGF-R antagonist is a tyrosine kinase inhibitor selective for EGF-R." As discussed above, the specification provides ample written description, including working examples, of EGF-R antagonists that are tyrosine kinase inhibitors selective for EGF-R. Accordingly, claims 26-36 meet the written description requirement of 35 U.S.C.§112, first paragraph.

Claims 26-36; enablement

The Office Action stated that the specification does not reasonably provide enablement for methods of treating nasal polyps comprising the administration of any EGF-R antagonist via any mode of administration. Applicants respectfully traverse the rejection.

*EGF-R antagonists*

The Office Action stated that the specification is enabling for a method of reducing goblet cell hyperplasia in an airway of an individual, comprising the administration of the EGF-R antagonist BIBX1522. The Office Action stated that the specification does not reasonably provide enablement for methods of treating nasal polyps comprising the administration of any EGF-R antagonist.

The specification provides ample description of EGF-R antagonists. Specification, page 8, paragraphs 46 to 50; and page 12, paragraph 68 to page 17, paragraph 89. Many of the EGF-R antagonists discussed in the specification are known to those skilled in the art. The general classes of EGF-R antagonists described in the specification include tyrosine kinase inhibitors, antibodies that bind a factor that stimulates EGF or EGF-R production, e.g., an antibody to TGF-α.

The specification provides **working examples** of *in vitro* and *in vivo* inhibition of mucin expression and airway mucus hypersecretion using BIBX1522, an EGF-R tyrosine kinase inhibitor. The specification also provides working examples of two additional EGF-R antagonists that are effective in reducing mucus hypersecretion. The specification further provides a working example showing that AG1478, another tyrosine kinase inhibitor that is an EGF-R antagonist, prevented MUC5AC synthesis induced by an activator of EGF-R, and inhibited EGF-R phosphorylation. Specification, e.g., Example 2. The specification further provides a working example showing that a TGF-α neutralizing antibody reduced production of goblet cells, which results in decreased mucus production. Specification, e.g., Example 3.

Thus, the specification provides three working examples of EGF-R antagonists that are efficacious in reducing mucus hypersecretion and goblet cell hyperplasia. EGF-R antagonists that are effective to reduce mucus hypersecretion and goblet cell hyperplasia are also effective to treat nasal polyps.

As shown in Example 8 (Specification, pages 70-75), the indicators of goblet cell hyperplasia and mucus hypersecretion, such as EGFR expression levels, TNF-α levels, and MUC5AC levels, are also present in nasal polyp epithelial cells. Thus, EGF-R antagonists that are effective to reduce mucus hypersecretion and goblet cell hyperplasia are also effective to treat nasal polyps.

Further evidence for the fact that EGF-R antagonists are effective in treating nasal polyps is provided in the Declaration of Jay Nadel under 37 C.F.R. §1.132 (the "Nadel Declaration"), provided herewith as Exhibit 1. The Nadel Declaration provides data showing the results of the EGF-R antagonist AG1478 on nasal epithelial cells obtained from nasal polyps from human patients. Nasal epithelial cells from nasal polyps were grown in *in vitro* culture. The cells were treated with TGF-α, a cytokine known to induce EGFR expression in human airway epithelium. In inhibition studies, cells were pretreated with the selective EGFR tyrosine kinase inhibitor AG1478. The level of mucin (MUC5AC) protein in the cells was assessed. Mucin staining was sparse in the control; TGF-α increased the number of mucin-

staining cells; and pretreatment of the cells with AG1478 completely inhibited TGF-α-induced mucin staining, while a control compound (AG9) did not inhibit TGF-α-induced mucin staining. These results indicate that a selective EGFR tyrosine kinase inhibitor reduces mucin induction in human nasal polyp epithelial cells.

*Routes of administration*

Applicants showed that systemic delivery of the EGFR antagonist BIBX1522 reduces airway goblet cell hyperplasia. Thus, those skilled in the art would reasonably expect that the same EGF-R antagonist or other EGF-R antagonists, when administered by other routes, e.g., via inhalation, would be efficacious, because administration by inhalation is administration directly at the site of the target cells (nasal epithelium).

Intratracheal instillation is a well-accepted model for delivery of a drug or other substance into the airways, and as such is a model of delivery by inhalation. Thus, a showing of activity of a given drug by intratracheal instillation is enabling for delivery by inhalation. Applicants showed that delivery of an EGF-R antagonist directly into the airways, by intratracheal instillation, reduces airway mucus hypersecretion (and therefore reduces goblet cell hyperplasia). When a drug is administered by intratracheal instillation, the site of the drug's action is via the airway lumen into airway epithelial cells.

In anesthetized small animals, stimuli and drugs delivered directly into the airways are often given by delivery of a small volume of drug via injection into the trachea (intratracheal instillation). During inspiration, the drug is carried into the lower airways. Where the amount of drug available for use in experimental animals is limited, or where it is important to know, as closely as possible, the amount of drug that is delivered to a small experimental animal, the drug is frequently delivered by intratracheal instillation. Intratracheal instillation is an art-accepted mode of airway delivery in small animal studies, and is accepted in the field as a model of airway delivery by inhalation.

Thus, Applicants have demonstrated that at least two different routes of administration – systemic and intratracheal (a model for delivery by inhalation) – are efficacious in reducing mucus hypersecretion and goblet cell hyperplasia.

*Reduction of mucus hypersecretion and reduction of goblet cell hyperplasia are correlative of reduction of nasal polyps.*

As shown in Example 8 (Specification, pages 70-75), the indicators of goblet cell hyperplasia and mucus hypersecretion, such as EGFR expression levels, TNF-α levels, and MUC5AC levels, are also present in nasal polyp epithelial cells. Thus, EGF-R antagonists that are effective to reduce mucus hypersecretion and goblet cell hyperplasia are also effective to treat nasal polyps.

Conclusion as to the rejection under 35 U.S.C. §112, first paragraph

Applicants submit that the rejection of claims 26-36 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

## III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSF-085CON5.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Aug. 3, 2007

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